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Factors associated with the clinical outcome and nephrotoxicity in patients treated with gentamicin

Wen-Hwei Chen
University of the Pacific

FACTORS ASSOCIATED WITH THE CLINICAL OUTCOME AND NEPHROTOXICITY IN PATIENTS TREATED WITH GENTAMICIN

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Wen-Hwei Chen

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Wen-Hwei Chen

is approved for recommendation to the Committee on Graduate Studies, University of the Pacific.

Department Chairman or Dean:

Donald L. Bailey

Thesis Committee:

Paul J. Williams Chairman

Patricia N. Catania

Coburn C. Ward

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INTRODUCTION

Gentamicin is a broad-spectrum antibiotic which belongs to the aminoglycoside group of antibiotics. It was first studied and described by Weinstein and co-workers[1] in 1963, and was then isolated, purified and characterized by Rosselot and colleagues[2] in 1964. Although newer members of the aminoglycoside antibiotics (e.g. tobramycin, amikacin, netilmicin and sisomycin) are now available, gentamicin remains the first line agent in the armamentarium against gram-negative bacterial infections.

Like other aminoglycoside antibiotics, gentamicin is rapidly bactericidal, it can be actively transported across the cell membrane and irreversibly bound to the bacterial ribosome, where it inhibits protein synthesis and decreases the fidelity of translation of the genetic codes. While limited in its action against most gram-positive bacteria, its antibacterial activity is primarily directed against aerobic, gram-negative bacilli. It has little activity against anaerobic microorganisms or facultative bacteria under anaerobic conditions.

Due to the highly polar cationic structure of gentamicin, it is very poorly absorbed from the gastrointestinal tract, but is completely absorbed after intravenous and intramuscular injection with the most common route being intermittent intravenous infusion.

Since gentamicin is water-soluble, it rapidly distributes into the extracellular fluid compartment. Because of its polar nature, gentamicin is largely excluded from the intracellular space; thus concentrations are low in most tissues and secretions. High concentrations can only be found in the renal cortex and in the endolymph and perilymph of the inner ear. This pattern of distribution presumably accounts for the nephrotoxicity and ototoxicity of gentamicin. Concentrations in the cerebral spinal fluid are also low, therefore intrathecal or intraventricular administration is necessary in cases of gram-negative bacillary central nervous system infections. There is negligible binding of gentamicin to plasma protein.[3]

Due to active hepatic secretion, the concentrations of gentamicin in the bile approach 30% of concomitant plasma concentrations; this represents a very minor excretory route. Gentamicin is excreted almost entirely by glomerular filtration, the renal clearance parallels the creatinine clearance and it may take as long as thirty days for complete recovery in urine. The plasma half-life is about two to three hours in patients with normal renal functions except for neonates. Since the pharmacokinetic parameters have a wide inter-individual variation, serum concentration determinations are essential for individual therapy to ensure the optimal use of this agent. Gentamicin is removed by hemodialysis as well as peritoneal dialysis. A supplemental dose therefore should be given after dialysis and frequent monitoring of concentrations in the plasma is important.

Although used for almost two decades, the factors associated with good clinical outcome and nephrotoxicity in patients receiving gentamicin therapy have not been definitively identified.

When gentamicin was first used, infective organisms were thought to influence the clinical outcome significantly.[4-6] Cox, et al.[4] found the bacterial eradication rate for Pseudomonas urinary tract infections (UTI's) was less than non-pseudomonal UTI's (74.2% vs. 97.1%, $p<0.05$). Shimizu[5] in a report of clinical experiences with gentamicin in Japan, also found that Pseudomonas and Proteus infections were cured less often than infections due to other microbes. Bodey, et al.[6] however found that Pseudomonas was not associated with a lower cure rate when compared with other microorganisms in cancer patients. Several other reports have similar results.[7-11] Bodey, et al. also found that infections due to Proteus species and Klebsiella-Enterobacter had a higher response rate (100% and 90%, respectively) when compared with other infections.

Site of infections has been identified as a factor influencing clinical outcome. Respiratory and biliary tract infections were found to have lower response rates than other infections by Shimizu[5] ($p<0.05$). Respiratory tract infections alone, however, did not show significant differences in terms of cure rates. Other investigators also found that pneumonias did not show significantly lower response rates.[6,7,13] UTI's, on the other hand, were shown to have a higher cure rate than

other infections in several different studies.[6,7,9] In addition, Bodey, et al.[6,7] found that cellulitis appeared to have a better cure rate as compared to other infections ($p<0.05$).

The relationship between the gentamicin serum concentrations and clinical response has also been studied. Jackson and Riff[12] reported that the persistence of pseudomonal bacteremia was inversely related to serum concentration. Seven of eight patients with peak concentrations of 2 mcg/ml or less had persistent bacteremia, whereas all six non-leukemic patients with peak concentrations of 4 mcg/ml or more had their bacteremic state eliminated ($p<0.05$). Noone, et al.[15] in the investigation of gentamicin therapy in gram-negative infections also reported that for UTI's, patients with peaks of 5 mcg/ml or more had a higher cure rate (17 of 18 or 94%) than patients with peak less than 5 mcg/ml (0 of 2 or 0%) ($p<0.05$). For the 15 episodes of wound infection, 12 were cured and a peak of 5 mcg/ml or more was achieved in all 15 episodes. For septicemia, 10 of 11 patients (91%) with peak of 5 mcg/ml or more were cured when compared to the 0% cure rate in the four patients with lower peak concentrations ($p<0.01$). For pneumonia patients, peak concentrations of 8 mcg/ml or more were achieved in 18 patients, of these 16 (89%) were cured; of the seven pneumonia patients whose peak concentrations were less than 8 mcg/ml, only three (43%) were cured ($P<0.05$). Moore, et al.[16] in a recent study of the association of aminoglycoside levels with mortality from gram-negative bacteremia showed that only one death (2.4%) occurred in 41 patients with initial

peak concentrations of greater than 5 mcg/ml of gentamicin or tobramycin and greater than 20 mcg/ml of amikacin as compared to the 20.9% mortality in the 43 patients with lower initial peak concentrations ($p<0.01$). When mean peak serum concentrations were compared, five deaths (8.3%) occurred in 60 patients with mean peak concentrations of greater than 5 mcg/ml of gentamicin or tobramycin and >20 mcg/ml of amikacin; and five deaths (20.8%) occurred in 24 patients with lower concentrations; this result was not statistically significant ($p>0.1$). Six deaths (13.0%) occurred in the 47 patients with initial trough aminoglycoside levels of greater than 2 mcg/ml of gentamicin and tobramycin, and of greater than 8 mcg/ml of amikacin; four deaths (11.0%) occurred in the 36 patients with lower trough levels, there was no significant association between initial trough levels and subsequent patient survival ($p>0.1$). On the other hand, other investigators found no correlation between serum concentrations and the clinical outcome in their patient populations with their serum concentrations less well defined.[10,17,18]

Minimal inhibitory concentrations (MIC's) of the pathogens have also been associated with clinical outcome. Athlin, et al.[10] stated that there was a positive correlation between low MIC and clinical improvement although the number of isolates were very small (seven isolated strains). Klastersky, et al.[8] found that of 101 patients with infections due to organisms that were inhibited by a concentration of 3 mcg/ml or less of antibiotics, 66 (65%) responded to therapy,

whereas only 23 of 42 (55%) infections caused by more resistant bacteria were cured, this difference, however, was not statistically significant ($p>0.1$). In a study of amikacin, Williams, et al.[19] found that the mean MIC was significantly higher in the patients who were not cured than in patients who were cured (8.8 ± 1.8 vs. 3.3 ± 0.3 mcg/ml, $p<0.05$). Parry, et al.,[13] on the other hand, stated that response was not related to pretreatment MIC's in patients receiving gentamicin and carbenicillin.

Serum antibacterial titer has also been studied[8] and correlated with clinical outcome. It was observed that of the 73 patients whose serum bacteriostatic titer was equal to or greater than 1:8, 56 (77%) responded to their antibiotic therapy, while only 33 (47%) of the 70 patients whose inhibitory titer was lower responded ($p<0.01$). The mean antibacterial activity in the urine of patients who were cured of urinary tract infections was also much higher than patients who were not cured (mean bateriostatic titer, 1:16 vs. 1:2; mean bactericidal titer 1:8 vs. 1:2); though no statistical test was performed. Reymann, et al.,[20] however, showed that a mortality of 32% (16 of 50) was found among those with a serum inhibitory level of less than 1:8 and a mortality of 37% (16 of 43) was found among those with an inhibitory level of 1:8 or more, this defference was not statistically significant ($p>0.5$).

There are discrepancies between the anticipated clinical response

rates and the ability of an antibiotic to inhibit bacterial growth. This may be partially explained by antibiotic synergism. Concomitant antibiotics therefore may be a factor positively correlated with clinical cure.

Bodey, et al.[6,7] in their studies of gentamicin treatment in cancer patients showed that initial neutrophil counts significantly influence the clinical cure rate. The response rate of gram-negative bacilli infections increased from 31% to 62% to 83% as the initial neutrophil counts increased from less than 100 to 101-1000 to greater than 1000 /mm^3 ($p<0.01$).

Parry, et al.[13] observed that the severity of underlying diseases, namely, nonfatal, ultimately fatal, and rapidly fatal according to the criteria set up by McCabe and Jackson[21] was related to the clinical outcome during gentamicin treatment. Twenty of twenty-one patients (95%) with nonfatal underlying diseases responded favorably to either tobramycin-ticarcillin or gentamicin-carbenicillin regimen, compared to 29 of 34 of patients (85%) with ultimately fatal and 18 of 27 patients (67%) with rapidly fatal underlying diseases ($p<0.05$). When investigating the relationship of severity of underlying diseases with the mortality in patients with gram-negative bacteremia, Moore, et al.[16] found a mortality rate of 67% in patients with rapidly fatal, 25% in patients with ultimately fatal and 8% in patients with nonfatal underlying diseases ($p=0.01$).

In terms of the toxicities induced by gentamicin, the incidence of nephrotoxicity is higher than ototoxicity. This may be partially due to the relative difficulty in assessing ototoxicity which requires the use of sequential audiogram and other tests that are not commonly performed in most clinical settings. Nephrotoxicity is usually assessed by monitoring various routine renal function tests such as serum creatinine changes. The incidence of aminoglycoside induced nephrotoxicity is approximately 8 to 26% of cases.[3] It is generally transient and non-oliguric in nature and is reversible in 90% of cases after the agent is discontinued. Several variables have been associated with gentamicin induced nephrotoxicity.

Host factors such as age, sex and pre-existing renal diseases have been studied. Kahlmeter, et al.[22] found that patients older than 60 years had a greater mean increment of serum creatinine at the end of gentamicin therapy (value not shown). Matzke, et al.[23] found that in patients receiving gentamicin via the dosing method of McHenry, the mean age of the nephrotoxic patients was significantly higher than the nontoxic patients (80.0 ± 2.9 vs. 59.0 ± 2.8, $p<0.05$). While in patients dosed according to Sawchuk and Zaske's method, the mean age was not significantly different between the toxic and nontoxic group. Taketomo, et al.[24] in a study of gentamicin nephrotoxicity also found that the mean age in the nephrotoxic group was significantly higher than the nontoxic group (65.6 ± 14.2 vs. 59.9 ± 16.3, $p<0.05$). Other studies have failed to find a correlation between age and nephrotoxicity.[25-31]

Kahlmeter, et al.[22] noted the increase in serum creatinine after gentamicin treatment was more pronounced in patients with initial creatinine clearance less than 70 ml/min/1.73 m^2 than patients with greater initial creatinine clearance (mean value not shown). Matzke, et al.[23] found that initial serum creatinine was significantly higher in the toxic patients group (mean of 1.48 mg/dl vs. 1.02 mg/dl, $p<0.01$). Taketomo, et al.[24] and Fee, et al.[25] confirmed this finding (Taketomo, et al.: mean of 1.2 vs. 1.0 mg/dl, $p<0.05$; Fee, et al.: mean of 1.16 vs. 0.88 mg/dl, $p<0.01$). Cabrera, et al.[26] in a study of the use of aminoglycosides in cirrhotic patients also found that when using urinary beta-2 microglobulin concentration greater than 3000 mcg/L as the criteria for nephrotoxicity, there was a significantly higher initial serum creatinine ($p<0.01$) and a lower initial creatinine clearance ($p<0.001$) in the nephrotoxic group. Interestingly, Moore, et al.[33] found that the initial creatinine clearance was higher in the nephrotoxic group ($p<0.05$). The explanation was that patients with higher creatinine clearances may have a higher filtered load of aminoglycosides and the proximal renal tubular cells may therefore be exposed to higher aminoglycoside concentrations, this then can lead to greater risks of nephrotoxicity. Still other studies indicate that there is no significant difference in the initial serum creatinine [27,28] or creatinine clearance[31,32] between toxic and nontoxic patients.

Most univariate studies[26,27,31] have not found any relationships

between sex and gentamicin nephrotoxicity . However, Moore, et al.[33] observed in their patient population treated with gentamicin or tobramycin that females had a higher incidence of nephrotoxicity than males although this was only of borderline statistical significance ($p=0.05$).

Several underlying disease states have been related to the development of nephrotoxicity. Reymann, et al.[20] in a study of patients receiving gentamicin or tobramycin found that volume depletion occurred more often in the nephrotoxic group (10 of 34) than the nontoxic group (4 of 67) ($p<0.01$). However, volume depletion occurred in five of the 13 patients with nephrotoxicity specifically induced by aminoglycosides and nine of the other 88 patients (5 of 21 patients with nephrotoxicity induced by other causes and 4 of 67 nontoxic patients), this difference was not statistically significant ($p>0.1$), thus the significance of the association between volume depletion and aminoglycoside induced nephrotoxicity was not established. Moore, et al.[33] found that shock and liver disease occurred more often in their nephrotoxic patients (30% vs. 12%, $p<0.05$ and 30% vs. 11%, $p<0.01$, respectively). Matzke, et al.[23] using pooled data from patients who received gentamicin or tobramycin, found the nephrotoxic group had a higher prevalence of congestive heart failure (data not shown, $p<0.05$). Rush, et al.[34] demonstrated a high prevalence of diabetes mellitus in patients with aminoglycoside nephrotoxicity, but there was no control group (i.e. patients who did not develop nephotoxicity). Moore, et al.[33] did not

find a statistical association between nephrotoxicity and diabetes mellitus.

Numbers of concomitant nephrotoxic drugs was found to be significantly greater ($p<0.05$) in the nephrotoxic patients in the study of Taketomo, et al.[24] Among these drugs, cephalosporins (especially cephalothin) and furosemide were two widely investigated agents in terms of their potential to enhance aminoglycoside nephrotoxicity and the results have been variable. Most studies[20,23,28-30,33,35] have failed to demonstrate the contribution of cephalosporins to gentamicin nephrotoxicity. However, Plager, et al.[36] found that on post-mortem examinations, patients who received cephalothin and gentamicin in combination had more tubular hydropic degeneration or acute tubular necrosis than patients who received gentamicin alone ($p<0.05$). Fong, et al.[30] when combining data of patients who received gentamicin or tobramycin, also found a significant association between concurrent cephalosporins and nephrotoxicity ($p<0.05$), but this association was not significant when looking separately at patients receiving either aminoglycoside alone. Studies regarding the effect of concomitant furosemide have also shown varying results. Most studies [20,26,28,30,35,37] did not find a significant correlation between furosemide and aminoglycoside nephrotoxicity except for one done by Schentag, et al.[31] They found in the nephrotoxic patients judged by 'clinical criteria' for nephrotoxicity (i.e. rise of serum creatinine of 0.5 mg% or more during therapy or within seven days of the last dose), there was a higher prevalence of concurrent diuretic use of which

96% was furosemide. Trollfors[38] has suggested that furosemide may potentiate the nephrotoxicity of gentamicin by reducing glomerular filtration rate.

Serum gentamicin concentrations (especially trough concentrations) have frequently been associated with the development of nephrotoxicity. Dahlgren, et al.[35] found that seven of 86 patients had a rise in serum creatinine during gentamicin therapy which promptly returned to normal upon discontinuation of treatment, and all of these seven patients had a trough concentration greater than 2 mcg/ml. None of the patients who did not have a rise in serum creatinine had a trough concentration greater than 2 mcg/ml, and this difference was significant ($p<0.005$). However, the time course of elevated serum creatinine and the rise of trough concentrations was not clear in this study, at least four of the seven patients had their elevated trough concentrations measured after there was a significant rise (>0.5 mg%) in serum creatinine. Therefore the elevated troughs could have been just a result of the already deteriorating renal function. Another study done by Goodman, et al.[32] reported that a trough of 4 mcg/ml or more was significantly associated with the development of nephrotoxicity. But the time course of rise in the serum creatinine and trough levels was not clear. Giamarellou, et al.[29] also found that trough concentrations of 2 mcg/ml or more was significantly associated with nephrotoxicity in gentamicin patients. Eight out of the 11 nephrotoxic patients had trough concentrations of 2 mcg/ml or more before the appearance of the nephrotoxicity. Taking only

these eight patients into consideration, there is still a significant association between the trough level of 2 mcg/ml or more and the nephrotoxicity. This association was confirmed in two other studies done by Matzke, et al.[23] and Cabrera, et al.[26]

Smith, et al.[27] in a study of patients treated with gentamicin or amikacin, found that the highest trough concentration prior to the rise in serum creatinine in the nephrotoxic group was significantly higher than the highest trough concentration in the nontoxic group ($p<0.05$ for the gentamicin group, and $p<0.01$ for the amikacin group). Taketomo, et al.,[24] instead of using actual trough levels, also found that estimated steady-state trough concentrations based on data obtained during the first three days of therapy were significantly higher in the nephrotoxic patients (mean values 1.9 vs. 1.5 mcg/ml, $p<0.05$).

Schentag, et al.[31] and Moore, et al.,[33] found that the initial trough concentrations were significantly higher in the nephrotoxic group than the nontoxic group (mean of 1.9 vs. 1.3 mcg/ml, $p<0.001$; mean of 3.4 vs. 2.6 mcg/ml, $p<0.05$, respectively). However, Smith, et al.[27] did not confirm this.

Peak gentamicin concentrations have also been investigated for their correlation with nephrotoxicity. Data from a study done by Smith, et al.[27] found five of 16 patients with peak concentrations of 10 mcg/ml or more developed nephrotoxicity, while only one of 39 patients with a

peak concentration of less than 10 mcg/ml developed nephrotoxicity ($p<0.01$). Giamarellou, et al.[29] also found that more nephrotoxic patients (5 of 17) than nontoxic patients (2 of 50) had peak concentrations of 10 mcg/ml or more ($p<0.05$). Matzke, et al.[23] on the other hand, found a higher mean peak level (7.3 ± 0.6 mcg/ml)in the nephrotoxic group than in the nontoxic group (5.8 ± 0.2 mcg/ml)($p<0.05$). Moore, et al.[16] stated the initial peak concentrations were significantly higher (7.2 ± 0.4 mcg/ml) in the nephrotoxic patients than in the nontoxic patients (5.3 ± 0.1 mcg/ml)($p<0.001$). Other studies[20,32] have not found a relationship between high peak levels and nephrotoxicity.

Other factors have also been considered to contribute to gentamicin nephrotoxicity. Taketomo, et al.[24] have noted that total dose of gentamicin throughout the treatment period was higher in the nephrotoxic group (mean of 1353 mg) than the nontoxic group (mean of 1025 mg) ($p<0.05$). Fee, et al.[25] similarly found that the toxic group had a mean total dose of 2.67 gm while the nontoxic group had a mean total dose of 1.64 gm and the difference was statistically significant($p<0.05$). Studies which did not find a significant association between the total dose and nephrotoxicity have also been presented.[23,27,28,31,33,35,36] Cabrera, et al.,[26] instead, found their nephrotoxic population had a significantly lower mean total dose (956 mg vs. 1582 mg, $p<0.01$). This was thought to be due to the dosage adjustment after the toxicity was identified.

Duration of therapy has also been demonstrated as a risk factor in gentamicin induced nephrotoxicity.[24,27-29] Smith, et al.[27] found that five of eight nephrotoxic patients received more than 11 days of gentamicin therapy while only 14 of 89 nontoxic patients had gentamicin treatment of more than 11 days ($p<0.01$). Giamarellou, et al.[29] found seven of 17 nephrotoxic patients as compared to nine of 50 nontoxic patients had gentamicin treatment for 10 or more days ($p<0.05$). Others found no significant difference in the duration of gentamicin treatment between nephrotoxic and nontoxic patients.[23,25,30-33,36]

The inconclusive results in the investigation of factors associated with clinical outcome or nephrotoxicity in gentamicin therapy as discussed above can at least be partially explained by the limitations of univariate analysis. Without controlling simultaneously other factors, univariate analyses may fail to accurately identify and interpret the factors associated with outcome. Further, a limited number of studies have employed the multivariate analytical methods.

Zaske, et al.[39] in the study of the treatment of burn patients with gentamicin used stepwise discriminant analysis to identify independent variables that were related to patient survival. Age, percent burn, individualized dosing, complication (yes/no) and bacteremia (yes/no) were included in the discriminant function to distinguish between patients survived or not throughout the entire hospital course. The discriminant functions however were not shown, and

no validation was done regarding the significance of this multivariate analysis.

In a study of patients receiving gentamicin or amikacin for gram-negative bacteremia, Moore, et al.[16] also utilized stepwise discriminant analysis to examine potential multivariate association between the mortality and various factors including age, sex, severity of underlying illness, serum creatinine concentrations, diabetes, peak temperatures, initial leukocyte counts, microbial etiology, concurrent antibiotics, suspected portal of entry and initial peak concentrations. It was found that severity of underlying illness, initial peak concentrations, initial leukocyte counts, and peak temperatures were included in the discriminant function for patient survival. The discriminant equations however were neither shown, nor was there any validation of the discriminant functions done.

For gentamicin nephrotoxicity, Prince, et al.[40] in the study of factors associated with creatinine clearance changes following gentamicin therapy, utilized forward stepwise multiple regression analysis. Using relative creatinine changes as the dependent variable, five independent variables were included into the regression equation, and the first three were clearly significant ($p<0.005$ for each step), these are peak gentamicin level, sex (female) and concomitant cephalothin. The authors explained the failure to detect a significant association between trough concentration and renal function changes by

the fact that some trough concentrations were below the sensitivity of the assay which may have obscured a stronger association. Also, the dosing regimen may have resulted in a relatively constant trough concentration among patients, therefore it may have failed to be detected in the regression analysis as a factor contributing to the renal function changes.

Taketomo, et al.[24] developed two discriminant functions to distinguish between nephrotoxic and nontoxic groups of patients receiving gentamicin, these models are as follows:

Model 1:

L = (0.12) T dur + (0.0021) II + (0.60) No. of concurrent nephrotoxic drugs - (0.93) complicating factors (yes/no) - 0.28

Model 2:

L = (-0.96) complicating factors (yes/no) + (0.56) No. of concurrent nephrotoxic drugs + (0.0054) D + (0.33) Cmin - 0.27

where the numbers in parentheses represent the unstandardized coefficients of the independent variables, and T dur is the duration of therapy (day); II is the 24 hour intensity index or the product of intensity factor (IF) and the number of doses per day; D is the total dose received (mg); Cmin is the estimated minimum serum

concentration of gentamicin (mcg/ml); nephrotoxic drugs include furosemide, cephalothin, cefazolin, tetracyclines, nafcillin, methicillin, cimetidine, amphotericin B and polymyxin; and complicating factors are factors that may result in renal impairment (e.g. septic or traumatic shock, hepatorenal syndrome secondary to alcoholism, uncontrolled hypertension, metastatic cancer, diabetes mellitus and drug overdose).

The probability of incorrect classification were 31.1% and 35%, respectively, for Models 1 and 2. Using cross-validation, it was shown that there were no significant differences between the original samples used to develop the discriminant functions and the hold out samples used to validate the developed functions.

More recently, Moore, et al.[33] similarly used discriminant analysis to develop an equation for classifying nephrotoxic and nontoxic patients receiving gentamicin or tobramycin. They established two discriminant functions, one using only those variables that can be obtained before treatment (Equation 1; Eq 1), the other using the factors known by 72 hours after treatment (Equation 2; Eq 2):

Eq 1:

L = (0.049) Age + (1.872) liver disease (yes =1, no =0) + (0.025) initial creatinine clearance + (1.102) Sex (men = 0, women = 1) - 5.098

Eq 2:

L = (0.333) initial 1-hour post dose level + (1.312) liver disease (yes = 1, no = 0) + (0.032) Age + (0.016) initial creatinine clearance + (0.739) Sex (men = 0, women =1) + (0.897) Shock (yes = 1, no = 0) - 5.357

By using the cumulative probability curve and a nomogram that was developed, the probability of developing nephrotoxicity can be determined for new cases. There was no information given on the percentage of correctly identified groups, but the authors have tested these two models in another independent validation population and found the mean scores in the nephrotoxic and nontoxic groups to be significantly different; Eq 2 being able to discriminate better than Eq 1. ($p<0.04$ for Eq 1; $p<0.005$ for Eq 2).

These multivariate analyses have made it possible to simultaneously take into consideration different variables associated with patients' outcome. Multiple regression relies on a single, continuous, dependent variable to define an outcome. Thus, it is probably not the most appropriate method to analyze a more sophisticated outcome such as clinical cure versus no cure or nephrotoxicity versus no toxicity. Since these outcomes depend on various criteria and since they are nominal in nature, discriminant analysis may appear to be more useful in identifying factors associated with these outcomes and thus identify patients who are at risk of nephrotoxicity or clinical failure.

This study is designed to investigate via discriminant analysis the factors that are associated with the clinical outcome and nephrotoxicity in patients receiving gentamicin.

METHODS

Patients

Medical records were retrospectively reviewed for 279 patients who received gentamicin as treatment and were being monitored by the pharmacokinetic service of St. Joseph's Hospital, Stockton, California between June 1984 and August 1985. Among these patients, 157 were excluded for the following reasons:

1. Younger than 18 years of age.
2. Had received less than three days of gentamicin therapy.
3. Lack of documented gram-negative infections.
4. Had an estimated creatinine clearance of less than 15ml/min/70kg.
5. Had received aminoglycoside therapy less than two weeks prior to the gentamicin therapy.

122 patients were included, 103 were used in the analyses for factors associated with clinical outcome and 120 were used for the study of factors associated with nephrotoxicity.

All patients received parenteral gentamicin as treatment for their infections. Dosage regimens were initially individualized based on physician's choice of loading dose and maintenance dose; serum

concentration monitoring was then implemented by the pharmacokinetic service of the pharmacy and was utilized as the basis of dosage adjustments to maintain peak serum concentrations in the range of 4 to 8 mcg/ml and trough concentrations below 2 mcg/ml. These adjustments were based on the methods described by Winter.[41]

Criteria and Definitions

Patients were classified as 'cure' if they remained afebrile (35.6° to 37.8°C) for four consecutive days without recurrent fever or until they were discharged without readmission, had no leukocytosis or signs of infections at the portal of entry (e.g. greater than 10^4 organisms/ml or greater than 10 white blood cells per high power field in the urine, new infiltrate of chest x-ray study, positive blood cultures or positive wound, bile or peritoneal fluid cultures) after the discontinuation of gentamicin. Patients who had positive evidence of any of the above signs or symptoms of infections were considered 'no cure'. Patients who had insufficient evidence to be classified as 'cure' or 'no cure' (e.g. lack of follow-up cultures in urinary tract infections) were excluded from the analyses for clinical outcome.

Patients were classified as nephrotoxic if during or within five days after the cessation of gentamicin therapy, they had a rise in serum creatinine of greater than 0.4 mg/dl when the baseline serum creatinine (serum creatinine within three days prior to or on the first day of

gentamicin therapy) was less than 3.0 mg/dl, or greater than 0.9 mg/dl if baseline serum creatinine was equal to or greater than 3.0 mg/dl.

Variables tested in the analyses for clinical outcome and nephrotoxicity studies are listed in Table 1 and Table 2.

Creatinine clearance was estimated by the modified method of Cockcroft and Gault[42] based on each patient's age, sex, weight and serum creatinine level. This will give an estimated creatinine clearance corrected to 70 kg of body weight.

Peak serum concentrations are defined as concentrations obtained 30 minutes after the cessation of the 30-minute infusion. While trough concentrations are the concentrations obtained within 30 minutes prior to the next dose. Initial peak and trough concentrations were taken at least after three or more doses of gentamicin. For the analyses of nephrotoxicity, total dose, duration of therapy, highest peak and trough concentrations were those calculated or obtained from the medical records until one day prior to the development of nephrotoxicity in the nephrotoxic patients; or those for the entire dosing period in the nontoxic patients.

Other concurrent effective antibiotics are the antibiotics used after microorganisms being treated have been shown to be sensitive in the <u>in vitro</u> sensitivity test and include cephazolin, cefoxitin,

Table 1. Variables used in the analyses of clinical outcome

Variables	Definition
sex*	female=0, male=1
age*	age in years
LUTI*	lower urinary tract infections (yes=1, no=0)
UUTI*	upper urinary tract infections (yes=1, no=0)
pneumonia*	pneumonia (yes=1, no=0)
bronchitis*	bronchitis (yes=1, no=0)
sepsis*	septicemia (yes=1, no=0)
wound*	wound infections (yes=1, no=0)
abdomen*†	abdominal infections (yes=1, no=0)
others†	other infections (yes=1, no=0)
multisite*	more than one infectious site (yes=1, no=0)
pseudo*	pseudomonal infection (yes=1, no=0)
multibug*	more than one infectious microorganisms (yes=1, no=0)
abx*	other concurrent effective antibiotics (yes=1, no=0)
op*†	surgical intervention (yes=1, no=0)
neutrophil*	initial neutrophil count in $10^3/mm^3$
tempmax	peak body temperature in degree Celcius
tdl	total dose of gentamicin in mg
durl	total duration of gentamicin therapy in days

Table 1. (continued)

Variables	Definition
pk0*	initial peak serum gentamicin concentration in mcg/ml
tr0*	initial trough serum gentamicin concentration in mcg/ml
pkmax1	highest peak serum gentamicin concentration in mcg/ml
trmax1	highest trough serum gentamicin concentration in mcg/ml

* the 48-hour variables

† variables not used in the analyses for medical patients

Table 2. Variables used in the analyses of nephrotoxicity

Variables	Definitions
sex*	female=0, male=1
age*	age in years
scr0*	baseline serum creatinine in mg/dl
crcl*	initial estimated creatinine clearance in ml/min/70kg
hypotn	presence of hypotension (yes=1, no=0)
cepha*	concurrent cephalosporins (yes=1, no=0)
lasix*	concurrent furosemide (yes=1, no=0)
toxins*	number of concurrent drugs with nephrotoxic potential other than cephalosporins and furosemide
td2	total dose in mg before nephrotoxicity is observed
dur2	duration of therapy in days before nephrotoxicity is observed
pk0*	initial peak serum gentamicin concentration in mcg/ml
tr0*	initial trough serum gentamicin concentration in mcg/ml
pkmax2	highest peak concentration in mcg/ml before nephrotoxicity is observed
trmax2	highest trough concentration in mcg/ml before nephrotoxicity is observed

* the 48-hour variables

cefamandol, cefotaxime, cefoperazone, ampicillin, carbenicillin, ticarcillin, piperacillin, and trimethoprim/sulfamethoxazole.

Patients were considered hypotensive if they had a diastolic blood pressure of less than or equal to 40 mmHg for two consecutive days. Shock was defined as a systolic pressure of less than 80 mmHg with a urine output of less than 500 ml/24 hr or a fall in the systolic blood pressure of greater than 50 mmHg if the final systolic pressure was below 100 mmHg.

Concomitant furosemide was only counted when furosemide was used before the observation of increasing serum creatinine to assure that furosemide is associated with the development instead of a result of nephrotoxicity.

Drugs other than cephalosporins and furosemide that were considered to have nephrotoxic potential are amphotericin B, sulfonamides (including trimethoprim/sulfamethoxazole), allopurinol, rifampin and ethambutol.

Statistical Analyses

Univariate analyses were conducted to compare between 'cure' and 'no cure' groups as well as nephrotoxic and nontoxic groups. Student's t-test was used to compare continous variables. Chi-square test was

used for discrete variables with Yate's correction if applicable. A p-value of 0.05 or less is considered to be statistically significant.

Stepwise discriminant analyses were used to discriminate between the 'cure' versus 'no cure' group as well as the 'toxic' versus 'nontoxic' group. A stepwise p-value of less than 0.05 was required for factors to enter the discriminant function. Discriminant analyses help to identify sets of variables that may be associated with nephrotoxicity as well as clinical failure, and they are also used in predicting future patients as 'cure' versus 'no cure' or 'toxic' versus 'nontoxic'.

The Jackknife procedure was used to estimate the error rate of the developed discriminant functions in classifying patients' outcomes. It is done by omitting one patient of the population from the discriminant analysis, the resultant discriminant function is used to classify the omitted patient and the result is recorded (i.e. correct or incorrect). Another patient is then excluded while the first patient is put back into the population, and the same procedure is repeated until all patients have been excluded from the analysis exactly once, then the overall misclassification result is the unbiased estimation of the true error rate of the discriminant function. Classification matrices of each model through the Jackknife procedure were also generated for the convenience of interpretation.

All statistical analyses were carried out using SPSS^{X} (Statistical

Package of the Social Science[X]) program which was available through the Computer Center, University of the Pacific, Stockton, California.

RESULTS

59 females and 63 males were entered into the retrospective study. The general demographic and pharmacokinetic descriptions are presented in Table 3 and 4.

Evaluation of Clinical outcome

It was possible to evaluate the clinical outcome in 103 patients (46 women and 57 men). Thirty-seven were classified as 'cure' while 66 were classified as 'no cure'. Patients were excluded when medical record data was insufficient to classify them as 'cure' or 'no cure'. The 19 patients who were excluded include 11 patients with lower UTI, two with upper UTI, two with pneumoia, two with bronchitis and one with a wound infection.

Comparisons between 'cure' and 'no cure' groups for individual demographic and pharmacokinetic parameters are presented in Table 5 and 6. Distribution of sites of infection was significantly different between the 'cure' and 'no cure' groups. The 'cure' group had a significantly higher percentage of septic patients as well as patients with abdominal infections ($p=0.001$ and $p<0.01$, respectively). Pneumonia patients had a lower cure rate than patients with other types of infections ($p<0.01$). Lower UTI was also found to occur less often in the 'cure' than the 'no cure' group though this was of borderline significance ($p=0.05$).

Table 3. Clinical descriptions of all patients--discrete variables

Discrete Variables	N
sex (male/female)	63/59
LUTI (yes/no)	27/95
UUTI (yes/no)	11/111
pneumonia (yes/no)	40/82
bronchitis (yes/no)	9/113
sepsis (yes/no)	24/98
wound (yes/no)	13/109
abdomen (yes/no)	11/111
others (yes/no)	2/120
multisite (yes/no)	16/106
abx (yes/no)	63/59
op (yes/no)	18/104
hypotn (yes/no)	6/116
cepha (yes/no)	46/76
lasix (yes/no)	46/76

Table 4. Clinical descriptions of all patients--continuous variables

Continous Variables	N	Mean ± SD*	Range
age (year)	122	65.1 ± 16.6	20 - 94
weight (kg)	119	64.7 ± 18.8	28 - 139
height (inch)	93	65.8 ± 5.0	48 - 86
neutrophil ($10^3/mm^3$)	116	9.68 ± 6.32	0.4 - 42.3
tempmax (^oC)	122	38.71 ± 1.00	37.0 - 41.3
toxins	122	0.1 ± 0.4	0 - 3
scr0 (mg/dl)	122	1.14 ± 0.50	0.3 - 3.8
crcl (ml/min/70kg)	122	72.9 ± 37.1	15 - 221
td1 (mg)	122	1689.3 ± 1134.6	380 - 7830
td2 (mg)	122	1638.0 ± 1113.7	160 - 7830
dur1 (day)	122	8.1 ± 4.2	3 - 27
dur2 (day)	122	7.8 ± 4.2	1 - 27
pk0 (mcg/ml)	117	4.75 ± 2.10	0.8 - 16.0
tr0 (mcg/ml)	118	1.48 ± 1.11	0.1 - 6.2
pkmax1 (mcg/ml)	78	6.36 ± 2.08	3.2 - 14.4
pkmax2 (mcg/ml)	73	6.08 ± 1.75	3.2 - 13.3
trmax1 (mcg/ml)	78	2.26 ± 1.42	0.5 - 7.3
trmax2 (mcg/ml)	74	1.97 ± 1.02	0.5 - 4.5

* mean ± standard deviation

Table 5. Univariate analysis of discrete variables of clinical outcome for all patients

Variables	Cure (n=37)	No Cure (n=66)	X^2	P
sex(female), n(%)	15 (40.5)	31 (47.0)	0.40	ns*
LUTI, n(%)	2 (5.4)	13 (19.7)	3.89	0.049
UUTI, n(%)	4 (10.8)	5 (7.6)	0.04†	ns
pneumonia, n(%)	7 (18.9)	31 (47.0)	8.01	0.005
bronchitis, n(%)	2 (5.4)	5 (7.6)	0.00†	ns
sepsis, n(%)	15 (40.5)	8 (12.1)	11.04	0.001
wound, n(%)	5 (13.5)	7 (10.6)	0.19†	ns
abdomen, n(%)	8 (21.6)	3 (4.5)	7.25†	0.007
others, n(%)	2 (5.4)	0 (0.0)	1.35†	ns
multisite, n(%)	4 (10.8)	11 (16.7)	0.65	ns
pseudo, n(%)	13 (35.1)	33 (50.0)	2.12	ns
multibug, n(%)	10 (27.0)	18 (27.3)	0.00	ns
abx, n(%)	20 (54.1)	35 (53.0)	0.01	ns
op, n(%)	12 (32.4)	4 (6.1)	12.57	0.0004

* not statistically significant

† with Yate's correction

Table 6. Univariate analysis of continuous variables of clinical outcome for all patients

Variables	Cure (n=37) (mean ± SEM)	No Cure (n=66) (mean ± SEM)	t	P
age (year)	63.7 ± 2.9	67.9 ± 1.7	1.32	ns*
neutrophil($10^3/mm^3$)	8.6 ± 0.8	9.8 ± 0.9	0.87	ns
tempmax (^oC)	38.6 ± 0.2	38.8 ± 0.1	1.01	ns
td1 (mg)	1788.8 ± 220.9	1724.2 ± 128.9	0.27	ns
dur1 (day)	7.9 ± 0.8	8.7 ± 0.5	0.85	ns
pk0 (mcg/ml)	4.3 ± 0.3	5.0 ± 0.3	1.33	ns
tr0 (mcg/ml)	1.3 ± 0.2	1.6 ± 0.2	1.51	ns
pkmax1 (mcg/ml)	3.5 ± 0.5	4.8 ± 0.4	1.86	0.066
trmax1 (mcg/ml)	1.3 ± 0.3	1.7 ± 0.2	1.15	ns

* not statistically significant

It was found that a significantly larger number of patients underwent a surgical procedure for their infections in the 'cure' group when compared with the 'no cure' group ($p<0.001$).

For the continuous numerical parameters, none was found to contribute significantly to the difference of the two groups.

Patients who did not undergo any surgical intervention have also been analyzed and have been denoted as medical patients. The medical patients consist of 25 'cure' and 62 'no cure' patients with their data presented in Table 7 and 8. Septic patients continued to show a higher cure rate than non-septic patients ($p<0.001$). Pneumonia patients did not have a lower cure rate ($p>0.05$). Highest peak plasma concentrations were significantly higher in the 'no cure' group ($p=0.05$). No other variables were found to differ significantly between the 'cure' and 'no cure' groups.

Multivariate stepwise discriminant analyses were further employed to develop models that could best describe the clinical outcome for all 103 patients. The models generated are shown in Table 9 and 10. From an initial entry of all variables listed in Table 1, surgical intervention, sepsis, peak body temperatures, initial peak concentration and age were sequentially included into the equation through the stepwise procedure. Among them, peak temperature, initial peak concentration and age have a negative discriminant coefficient which

Table 7. Univariate analysis of discrete variables of clinical outcomes for medical patients

Variables	Cure (n=25)	No Cure (n=62)	X^2	P
sex(female), n(%)	11 (44.0)	29 (46.8)	0.06	ns*
LUTI, n(%)	2 (8.0)	13 (21.0)	1.29†	ns
UUTI, n(%)	4 (16.0)	5 (8.1)	0.51†	ns
pneumonia, n(%)	7 (28.0)	30 (48.4)	3.03	0.08
bronchitis, n(%)	2 (8.0)	5 (8.1)	0.00†	ns
sepsis, n(%)	12 (48.0)	7 (11.3)	14.06	0.0002
wound, n(%)	3 (12.0)	7 (11.3)	0.01†	ns
multisite, n(%)	3 (12.0)	11 (17.7)	0.11†	ns
pseudo, n(%)	11 (44.0)	33 (53.2)	0.61	ns
multibug, n(%)	6 (24.0)	16 (25.8)	0.03	ns
abx, n(%)	14 (56.0)	34 (54.8)	0.01	ns

* not statistically significant

† with Yate's correction

Table 8. Univariate analysis of continous variables of clinical outcomes for medical patients

Variables	Cure (n=25) (mean ± SEM)	No Cure (n=62) (mean ± SEM)	t	P
age (year)	65.8 ± 3.4	68.0 ± 1.7	0.63	ns*
neutrophil ($10^3/mm^3$)	8.6 ± 0.8	9.7 ± 1.0	0.65	ns
tempmax (^oC)	38.7 ± 0.2	38.8 ± 0.1	0.43	ns
td1(mg)	1861.8 ± 300.3	1727.4 ± 130.8	0.48	ns
dur1 (day)	8.6 ± 1.0	8.7 ± 0.5	0.10	ns
pk0 (mcg/ml)	4.6 ± 0.3	4.9 ± 0.3	0.51	ns
tr0 (mcg/ml)	1.4 ± 0.2	1.6 ± 0.2	0.83	ns
pkmax1 (mcg/ml)	3.3 ± 0.6	4.9 ± 0.4	1.99	0.05
trmax1 (mcg/ml)	1.2 ± 0.3	1.8 ± 0.2	1.47	ns

* not statistically significant

Table 9. Discriminant analysis of clinical outcome for all patients--

Model C1--all variables

Variables Included	Discriminant Coefficient	Group centroids (L)* Cut-off point (C)	Canonical Correlation	Jackknife*†§ Classification
op	1.840	L_0 = -0.4631	0.5298	
sepsis	2.015	L_1 = 0.8261		
tempmax	-0.5085			
pk0	-0.1020	C = 0.1815		
age	-0.01488			
constant	20.45			

	D_0	D_1	
G_0	52	14	66
G_1	14	23	37
	66	37	103

$P(D_0/G_0)$=78.8%
$P(D_1/G_1)$=62.2%
$P(G_0/D_0)$=67.6%

* 0 = no cure, 1 = cure

† prior probabilities of cure and no cure are both 50%

§ D = group classified by discriminant function, G = actual group

$P(D_0/G_0)$ = the probability that the model can identify a patient to be 'no cure' given that the patient is not cured

$P(D_1/G_1)$ = the probability that the model can identify a patient to be 'cure' given that the patient is cured

$P(G_0/D_0)$ = the probability of the patient becoming not cured given that the model predicts so

Table 10. Discriminant analysis of clinical outcome for all patients--Model C2--48-hour variables

Variables Included	Discriminant Coefficient	Group Centroids (L)* Cut-off point (C)	Canonical Correlation	Jackknife*†§ Classification
op	2.097	L_0 = -0.4200	0.4929	
sepsis	2.099	L_1 = 0.7492		
wound	0.8433			
abx	-0.4797	C = 0.1646		
constant	-0.6366			

	D_0	D_1	
G_0	52	14	66
G_0	12	25	37
	64	39	103

$P(D_0/G_0)$=78.8%
$P(D_1/G_1)$=67.6%
$P(G_0/D_0)$=70.8%

* 0 = no cure, 1 = cure

† prior probabilities of cure and no cure are both 50%

§ D = group classified by discriminant function, G = actual group

$P(D_0/G_0)$ = the probability that the model can identify a patient to be 'no cure' given that the patient is not cured

$P(D_1/G_1)$ = the probability that the model can identify a patient to be 'cure' given that the patient is cured

$P(G_0/D_0)$ = the probability of the patient becoming not cured given that the model predicts so

means a negative association with clinical cure since the mean discriminant score (or group centroid) of the 'cure' group is a positive value of 0.826 and the centroid of the 'no cure' group is a negative value of -0.463.

Jackknife classification results showed that 52 out of 66 'no cure' patients and 23 out of 37 'cure' patients were correctly identified. By applying Bayes' rule, the probability of correctly predicting a patient to be not cured is 67.6% compared to the a priori probability of 50%.

Similarly, another model was developed using variables available within 48 hours after the initiation of gentamicin therapy (the 48-hour variables in Table 1). As seen in Table 10, Model C2, surgical intervention and sepsis again were the first two variables that entered the model; wound infections and other concurrent effective antibiotics then entered subsequently. Only 'other concurrent effective antibiotics' has a negative discriminant coefficient. The centroids of the 'cure' and the 'no cure' groups are 0.749 and -0.420, respectively. Jackknife classification shows that 78.8% (52/66) of 'no cure' patients and 67.6% (25/37) of 'cure' patients were correctly identified and probability of the model to correctly predicting a patient to be not cured is 70.8% according to Bayes' rule.

For medical patients, results of discriminant analyses are shown

Table 11. Discriminant analysis of clinical outcome for medical patients--Model C3--all variables

Variables Included	Discriminant Coefficient	Group centroids (L)* Cut-off point (C)	Canonical Correlation	Jackknife*†§ Classification
sepsis	-2.902	L_0 = 0.3546	0.4918	
pkmax1	0.09800	L_1 = -0.8793		
tempmax	0.4593			
age	0.02007	C = -0.2624		
UUTI	1.0181			
constant	-19.08			

	D_0	D_1	
G_0	50	12	62
G_1	11	14	25
	61	26	87

$P(D_0/G_0)$=80.6%
$P(D_1/G_1)$=56.0%
$P(G_0/D_0)$=64.7%

* 0 = no cure, 1 = cure

† prior probabilities of cure and no cure are both 50%

§ D = group classified by discriminant function, G = actual group

$P(D_0/G_0)$ = the probability that the model can identify a patient to be 'no cure' given that the patient is not cured

$P(D_1/G_1)$ = the probability that the model can identify a patient to be 'cure' given that the patient is cured

$P(G_0/D_0)$ = the probability of the patient becoming not cured given that the model predicts so

Table 12. Discriminant analysis of clinical outcome for medical patients--Model C4--48-hour variables

Variables Included	Discriminant Coefficient	Group centroids (L)* Cut-off point (C)	Canonical Correlation	Jackknife*†§ Classification
sepsis	3.143	L_0 = -0.3033	0.4351	
UUTI	-1.151	L_1 = 0.7521		
abx	-0.5898			
constant	-0.2418	C = 0.2244		

	D_0	D_1	
G_0	50	12	62
G_1	7	18	25
	57	30	87

$P(D_0/G_0)$=80.6%
$P(G_1/D_1)$=72.0%
$P(G_0/D_0)$=74.2%

* 0 = no cure, 1 = cure

† prior probabilities of cure and no cure are both 50%

§ D = group classified by discriminant function, G = actual group

$P(D_0/G_0)$ = the probability that the model can identify a patient to be 'no cure' given that the patient is not cured

$P(D_1/G_1)$ = the probability that the model can identify a patient to be 'cure' given that the patient is cured

$P(G_0/D_0)$ = the probability of the patient becoming not cured given that the model predicts so

in Table 11 and 12. From an initial entry of all variables in Table 1 except abdominal infections, other infections and surgical intervention, the following variables were included in Model C3: sepsis, highest peak serum concentration, peak temperatures, age and upper UTI. Sepsis, upper UTI and other concurrent effective antibiotics were included in Model C4 when only the 48-hour variables were tested. From the discriminant coefficient of each variable and the mean discriminant score of each group, sepsis was again found positively correlated with clinical cure when other variables in the model are controlled, while all other factors in these models appeared to correlate with clinical cure negatively. Jackknife classification shows the probability of correctly classifying 'no cure' patients is 80.6% for both models, and the probability of correctly predicting a new patient not to be cured is 64.7% for Model C3 and 74.2% for Model C4, compared to the a priori probability of 50%.

Evaluation of Nephrotoxicity

One hundred and twenty patients were evaluated for nephrotixicity. One patient was excluded due to incomplete serum creatinine information while another was excluded because an episode of septic shock complicated the evaluation of the presence of gentamicin induced nephrotoxicity.

Thirteen of the 120 patients were classified as nephrotoxic. In

Table 13. Univariate analysis of discrete variables for nephrotoxicity for all patients

Variables	Nontoxic (n=107)	Toxic (n=13)	X^2	P
sex(female), n(%)	55 (51.4)	3 (23.1)	3.72	0.05
hypotn, n(%)	5 (4.8)	1 (7.7)	0.00*	ns†
cepha, n(%)	39 (36.4)	6 (46.2)	0.14*	ns
lasix, n(%)	37 (34.6)	8 (61.5)	2.53*	ns

* with Yate's correction

† not statistically significant

Table 14. Univariate analysis of continuous variables for nephrotoxicity for all patients

Variables	Nontoxic (n=107) (mean ± SEM)	Toxic (n=13) (mean ± SEM)	t	P
age (year)	64.3 ± 1.7	70.2 ± 2.4	1.20	ns*
scr0 (mg/dl)	1.1 ± 0.1	1.2 ± 0.2	0.59	ns
crcl (ml/min/70kg)	73.6 ± 3.5	72.2 ± 12.3	0.13	ns
toxins	0.14± 0.04	0.15± 0.10	0.11	ns
td2 (mg)	1672.9 ± 109.8	1430.8 ± 274.9	0.73	ns
dur2 (day)	8.0 ± 0.4	6.7 ± 1.3	1.04	ns
pk0 (mcg/ml)	4.3 ± 0.2	6.9 ± 1.1	4.13	0.000
tr0 (mcg/ml)	1.3 ± 0.3	2.1 ± 0.4	2.25	0.026
pkmax2 (mcg/ml)	3.5 ± 0.3	4.0 ± 1.2	0.52	ns
trmax2 (mcg/ml)	1.2 ± 0.1	1.1 ± 0.4	0.14	ns

*: not statistically significant

the univariate analyses as shown in Tables 13 and 14, females had a borderline lower incidence of nephrotoxicity ($p=0.05$). Initial peak ($p<0.001$) and trough ($p<0.05$) concentrations are both significantly higher in the toxic group. No other variables tested showed significant differences between toxic and nontoxic patients.

When all variables listed in Table 2 were used in the stepwise discriminant analysis to develop a discriminant function, Model N1 in Table 15 resulted. Ten steps were performed while eight variables were included in the model. The eight variables entered in the model include initial peak concentration, sex, baseline creatinine clearance, concomitant furosemide, concomitant cephalosporins, age, highest trough concentrations and initial trough concentration. Duration of therapy was entered at step 4 but was found to be excluded again at step 10 when it was detected to have failed to contribute to the discriminant function significantly. Because this equation is awkward for classifying patients, the Jackknife classification procedures were not performed. Instead, a second analysis using 48-hour variables was attempted.

As seen in Model N2 (Model 15), a much simpler model resulted. From the initial entry of the 48-hour variables in Table 2, initial peak concentration, sex, initial creatinine clearance, concomitant cephalosporins and age sequentially entered the model and all are with a positive correlation with nephrotoxicity. Jackknife procedure shows

Table 15. Discriminant analysis of nephrotoxicity--

Model N1--all variables

Variables Included	Discriminant Coefficient	Group centroids (L)* Cut-off point (C)	Canonical Correlation	Jackknife Classification
pk0	0.3569	L_0 = -0.2002	0.5012	---
sex	1.051	L_1 = 1.648		
crcl	0.01874			
lasix	0.6841			
cepha	0.4674			
age	0.01694			
trmax2	-0.4148			
tr0	0.4215			
constant	-5.211			

* 0 = nontoxic, 1 = toxic

Table 16. Discriminant analysis of nephrotoxicity--

Model N2--48-hour variables

Variables Included	Discriminant Coefficient	Group centroids (L)* Cut-off point (C)†	Canonical Correlation	Jackknife*†§ Classification
pk0	0.4488	L_0 = -0.1752	0.4520	a.†
sex	1.140	L_1 = 1.442		
crcl	0.01562			
cepha	0.5940	C_a = 1.937		
age	0.01883	C_b = 0.6334		
constant	-5.246			

	D_0	D_1	
G_0	105	2	107
G_1	10	3	13
	115	5	120

$P(D_0/G_0)$=98.1%
$P(D_1/G_1)$=23.1%
$P(G_1/D_1)$=60.0%

b.†

	D_0	D_1	
G_0	86	21	107
G_1	6	7	13
	92	28	120

$P(D_0/G_0)$=80.4%
$P(D_1/G_1)$=53.8%
$P(G_1/D_1)$=73.3%

* 0 = nontoxic, 1 = toxic

† a = prior probability of nephrotoxicity = 10.8%, b = 50.0%

§ D = group classified by discriminant function; G = actual group

$P(D_0/G_0)$ = the probability that the model can identify a patient being nontoxic given that the patient is nontoxic

$P(D_1/G_1)$ = the probability that the model can identify a patient being toxic given that the patient is toxic

$P(G_1/D_1)$ = the probability of a patient becoming toxic given that the model predicts so

that when the prior probability is chosen to be 10.8% based on the actual size of toxic patients in the patient population, there is a 23.1% probability of correctly identifying a nephrotoxic patient. In the meantime, there is a 60.6% probability of correctly predicting a patient to be nephrotoxic.

Due to the fact that 76.9% of the nephrotoxic patients were actually misclassified ($P(D_1/G_1)$=23.1%), the prior probability of nephrotoxicity was raised to 50%. This resulted in an increased sensitivity of the model to detect nephrotoxic patients (53.8%) although it also sacrificed the accuracy in classifying nontoxic patients from 98.1% to 80.4%. The probability of correct prediction of a new patient to be nephrotoxic became 73.3% based on Bayes' rule as opposed to the 50% prior probability.

A third model, Model N3 (Table 17), was developed when sex was excluded from the 48-hour variables. This model included the variables of initial peak concentration, initial creatinine clearance, concurrent furosemide and age. The probability of correctly classifying a nephrotoxic patient is 15.4% when the prior probability of nephrotoxicity is chosen to be 10.8%. This improved and became 46.2% when 50% is used as the prior probability of toxicity. When the canonical correlation coefficients which measure the correlation between the discriminant function and the differences between the two groups were compared, Model N3 had a weaker discriminant power than Model N2.

Table 17. Discriminant analysis of nephrotoxicity--

Model N3--48-hour variables excluding sex

Variables Included	Discriminant Coefficient	Group centroids (L)* Cut-off point (C)†	Canonical Correlation	Jackknife*†§ Classification
pk0	0.4381	L_0 = -0.1494	0.3967	a.†
crcl	0.01532	L_1 = 1.2295		
lasix	0.6033			
age	0.02002	C_a = 2.069		
constant	-4.666	C_b = 0.5401		

	D_0	D_1	
G_0	105	2	107
G_1	11	2	13
	116	4	120

$P(D_0/G_0)$=98.1%
$P(D_1/G_1)$=15.4%
$P(G_1/D_1)$=50.0%

b.†

	D_0	D_1	
G_0	84	23	107
G_1	7	6	13
	91	29	120

$P(D_0/G_0)$=78.5%
$P(D_1/G_1)$=46.2%
$P(G_1/D_1)$=68.2%

* 0 = nontoxic, 1 = toxic

† a = prior probability of nephrotoxicity = 10.8%, b = 50.0%

§ D = group classified by discriminant function; G = actual group

$P(D_0/G_0)$ = the probability that the model can identify a patient being nontoxic given that the patient is nontoxic

$P(D_1/G_1)$ = the probability that the model can identify a patient being toxic given that the patient is toxic

$P(G_1/D_1)$ = the probability of a patient becoming toxic given that the model predicts so

For the convenience of future classification, a cumulative probability curve for Model N2 with 50% prior nephrotoxicity probability was developed (Figure 1). By calculating a new patient's discriminant score and plotting it on the abscissa then projecting it onto the curve, the probability of the patient developing nephrotoxicity can be estimated from the ordinate. This curve provides an alternative patient classification method, instead of using a fixed cut-off point and rigidly assigning patients dichotomously into the nephrotoxic or nontoxic group, the likelihood of a patient developing nephrotoxicity can now be found.

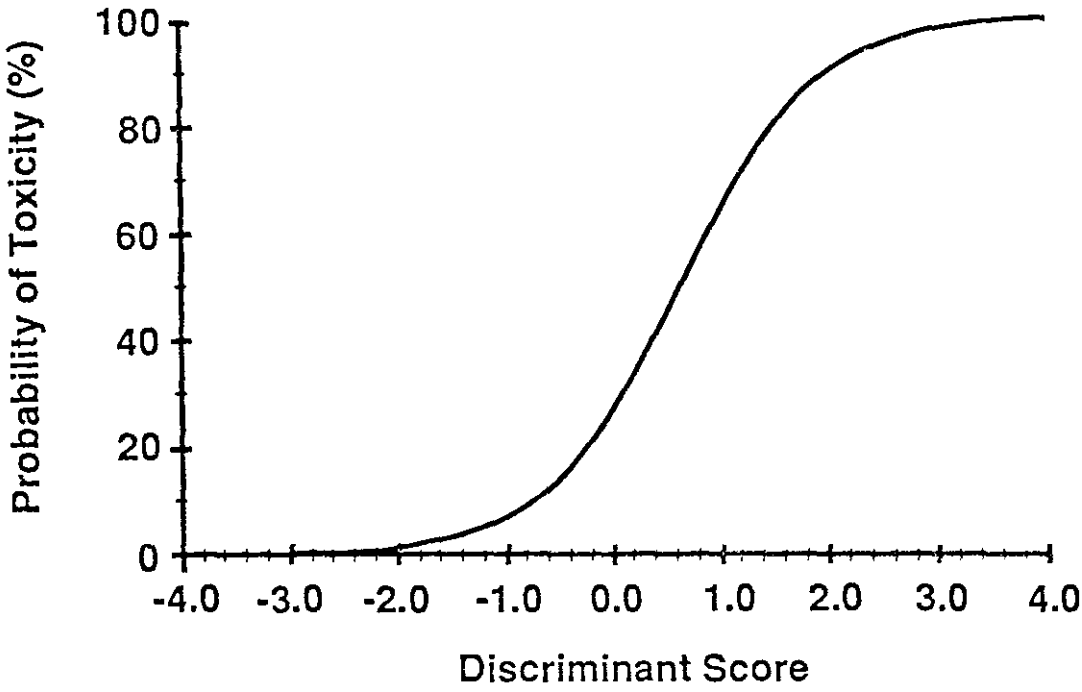

Fig. 1. Expected probabilty of nephrotoxicity development given the discriminant scores based on Model N2 and an a priori probability of nephrotoxicity of 50%.

DISCUSSION

Factors associated with clinical outcome and nephrotoxicity in patients receiving aminoglycoside antibiotics continue to be controversial. Although many researchers have tried to define the relationship of various demographic and pharmacokinetic variables to clinical outcome or nephrotoxicity, the results have been inconsistent.

The inconsistency of the previous studies may be explained by the utilization of univariate statistical analyses. This study thus utilized both univariate and multivariate techniques in an attempt to better define the factors associated with the clinical outcome and nephrotoxicity in patients receiving gentamicin.

The discrepancies between the univariate and multivariate analyses are apparent in the analyses for clinical outcome. More pneumonia patients had clinical failure in the univariate analysis for all patients, this is consistent with some earlier reports.[5] This site of infection ceased to contribute to the difference of clinical outcome when stepwise discriminant analysis was done. The reason for this discrepancy is not clear since pneumonia was not found to correlate with any other tested variables significantly. One possible explanation is that other underlying factors which were not tested in this study may in fact correlate with pneumonia and contribute significantly to the difference between the 'cure' and 'no cure' groups; while in the

discriminant model developed, pneumonia per se could not contribute significantly to this difference thus was left out of the model.

The prevalence of abdominal infections also appears to be significantly greater in the 'cure' than 'no cure' groups. When the correlation matrix of all variables tested were examined, a high correlation between abdominal infections and surgical intervention was found (r=0.79). Therefore, when surgical intervention was in the model, 'abdominal infections' was not able to provide additional significant information to the discriminant model.

Factors tested and found not to differ significantly between 'cure' and 'no cure' groups in the univariate analyses and yet were included in Model C1 are peak temperature, age and initial peak concentration. Since the mean discriminant score or centroid of the 'cure' group is a positive value, the negative discriminant coefficients of peak temperature and age suggest a negative correlation with clinical cure. That is, the older the patient or the higher the body temperature, the less likely that the patient was cured. It is, however, hard to explain the negative correlation between initial peak concentration and clinical cure except that this may have reflected the more aggressive treatment initially in patients who had more critical clinical status.

Two factors have consistently appeared in both the univariate and

discriminant analyses for Models C1 and C2, one being surgical intervention, the other, sepsis. Both of these variables were found to correlate positively with clinical cure. Surgical intervention is a routine treatment in disease states such as appendicitis, cholecystitis and abscesses. Antibiotics in these cases often only play an auxiliary role. Therefore, in the absence of post-operative complications, surgical intervention can be expected to correlate positively with clinical cure.

The reason for a positive correlation between sepsis and clinical cure is not readily apparent. It was suspected that septic patients may have received more aggressive treatment in terms of their duration of therapy, total dose or serum concentrations. However, a univariate comparison and the multivariate correlation matrix have both failed to find any evidence indicating that this was the case. It was also possible that in some of the septic patients (10/23), no focus of infection was identified, therefore based on the criteria of clinical cure, only the systemic signs and symptoms of sepsis and blood cultures can be evaluated. The possible presence of occult infections at the focus may have been overlooked and some of these patients may have been falsely classified as 'cure'.

When the 48-hour variables were analyzed in Model C2, surgical intervention, sepsis, wound infections and other concurrent effective antibiotics were included besides the aforementioned surgical

intervention and sepsis. 'Wound infections' is positively correlated while other 'concurrent effective antibiotics' is negatively correlated with clinical cure. It was found that in the univariate analysis, the 'cure' group has slightly higher rather than lower percentage of patients treated with concurrent effective antibiotics although this was not statistically significant. The negative discriminant coefficient thus can only be explained by some unknown correlation of the concurrent antibiotics with the other variables already in the models. The clinical significance of this observation is of questionable value.

Since surgical intervention was consistently the first variable to enter the discriminant function during the stepwise procedure while surgery itself may be a decisive factor for clinical outcome, we decided to evaluate patients who did not undergo any surgery.

The variables included in Models C3 and C4 overlapped with Models C1 and C2 with only 2 exceptions. The variables that overlapped between C3 and C1 include sepsis, peak temperature and age while the highest peak concentration instead of initial peak concentration was included in Model C3. Upper UTI is another new variable appeared in Model C3. Variables overlapped between Models C4 and C2 include sepsis and other effective antibiotics. But upper UTI rather than wound infections was enterd into Model C4 as compared to Model C2. This indicates that although surgical intervention played an important role in contribuing to patients' cure, the other factors that influenced the results of

gentamicin treatment are essentially the same for all patients. Both the highest peak concentration in Model C3 and the initial peak concentrations in Model C1 are negatively correlated with clinical cure and this probably is a result rather than a cause of clinical failure.

Upper UTI was included in both Models C3 and C4 and it has an apparently negative association with clinical cure. Interestingly, in the univariate comparison of the 'cure' and 'no cure' groups, the 'cure' group actually had a higher percentage of patients with upper UTI. By further investigation of the correlation between each pair of variables in the analysis, it was found that upper UTI has a relatively high positive correlation with sepsis ($r=0.55$). Thus, when sepsis was previously in the model, upper UTI ceased to contribute positively to a significant extent to clinical cure, that is, when sepsis and other variables already in the model are controlled for, upper UTI contributes negatively to clinical outcome which was masked in the univariate analysis. Although this can technically explain the apparent differences between the univariate and multivariate models, the true relationship of upper UTI and clinical outcome in the population is not clear.

It was hoped that through these analyses, factors that can be easily monitored and controlled through the treatment period could be identified to increase the probability of clinical cure. From the results, surgical intervention played an important role in determining

clinical outcome. Older patients and those with higher temperatures were at higher risks of treatment failure. However, parameters that were used to attempt to reflect the aggressiveness of the treatment, such as serum gentamicin concentrations, duration of therapy, total dose and other concurrent effective antibiotics, were not demonstrated to increase the probability of clinical cure. In this study, none of the serum concentration measurements have been positively associated with cure. This may have been due to the fact that for most patients, the peak serum concentrations were in the 4 to 8 mcg/ml range via the pharmacokinetic service. Noone, et al.[15] had suggested that cure rate would be higher if peak concentration is above 5 mcg/ml for most infections. Since the patients had serum concentrations maintained within this therapeutic peak range, the small differences in the peak concentrations probably would not discriminate between clinical outcomes.

There are other variables which were reported to contribute to clinical outcome in patients treated with aminoglycosides and yet not included in this study. Severity of underlying diseases have been shown to influence clinical outcome in some studies.[12,13] The failure to include this variable in the study may have diminished the ability to dicriminate between the 'cure' and 'no cure' groups. Williams, et al.[19] in a recent study of patients treated with amikacin have reported that MIC, intensity factors which also requires the knowledge of MIC, and the ratio of mean peak concentration and MIC all correlate significantly

with patients' clinical outcome in the discriminant analysis. In a retrospective study done by Deziel-Evans, et al.,[43] several pharmacokinetic indices which constituted certain measurement of serum concentration relatively to MIC were all found to correlate positively with clinical outcome. Due to the lack of routine measurement of MIC in this hospital setting where the data was obtained, it was not possible to include any variable relating to MIC in the analyses. While this study included the most commonly obtainable variables in a community hospital setting and while the discriminant functions developed did disclose some correlation between these variables and clinical outcome, the inclusion of MIC related variables and underlying diseases may have changed the results.

Besides the identification of potential discriminators of two distinct groups, discriminant functions can also be used to classify new patients. With all the aformentioned models in the study, an unbiased statistical method, namely, the Jackknife procedure was utilized to validate the models. This procedure is used to estimate the accuracy of these models to classify the original patients as well as to predict new patients' outcomes. The latter is estimated based on the application of Bayes' rule.

For models of clinical outcome, since the prior probability of clinical outcome is both 50%, the classification cut-off point is the point half-way between the mean discriminant score (group centroid) of

each group. By calculating each patient's discriminant score, it can then be compared with the cut-off point and the patient can be classified or predicted to be cured or not cured. Let D_0 represent that the patient is classified to be 'no cure' based on the discriminant score and G_0 represent that the patient is truly a 'no cure' patient, then $P(D_0/G_0)$ shows the sensitivity of the discriminant model to identify a patient who is known to be 'no cure'. Similarly, $P(D_1/G_1)$ shows the sensitivity of the model to identify a known cured patient where D_1 represents that the patient is classified as 'cure' based on the discriminant score and G_1 represents that a patient is known to be cured. $P(G_0/D_0)$, on the other hand, shows the probability of the model to correctly predict a new patient to have a clinical failure. All four models (C1 to C4) were able to identify 'no cure' patients more readily than the 'cure' patients (i.e. $P(D_0/G_0) > P(D_1/G_1)$). All models can improve the accuracy of predicting a new patient to be 'no cure' (i.e. $P(G_0/D_0)$) by 15 to 25% compared to the a priori probability of 50%.

By examining the canonical correlation coefficients which represent the correlation of each model with the differences of the two groups, it was found that none of the models explained more than 30% of the differences of the two groups (squared value of the canonical correlation). Therefore although the models developed do serve as tools to identify some factors that are associated with clinical outcome in patients treated with gentamicin, and can improve the prediction of the

patients' clinical outcomes, they can only explain partially the differences between patients that have clinical cure and failure. As suggested by other studies, some more sophisticated pharmacokinetic variables such as intensity index, ratio of peak serum concentration to MIC as well as the consideration of severity of underlying disease states need to be considered to improve further the discrimination.

In the analyses for risk factors of gentamicin nephrotoxicity, 10.8% of our patients were defined as having developed nephrotoxicity which is consistent with the approximate population incidence of 8 to 26%.[3]

Besides the univariate analyses, three discriminant models were developed. Model N1 was developed based on the entry of all variables in Table 2. Of the three concentration measurements in the model, there is a relatively high correlation between highest trough concentration with both the initial peak (r=0.364) and initial trough (r=0.531), it is therefore hard to interpret the signs of these coefficient terms. Models N2 and N3 were then developed based on fewer variables that were obtained within the first 48 hours of gentamicin therapy.

From both the univariate and the multivariate analysis, the initial peak serum concentration of gentamicin shows a strong correlation with the development of nephrotoxicity. This finding is consistent with several previous studies.[33,40] The initial trough

concentration, although found to differ significantly (p=0.026) in the univariate comparison between toxic and nontoxic groups, was included in only the discriminant function Model N1. In Model N1 where all possible variables were tested, eight variables entered the model with the initial peak concentration as the first variable entered, while initial trough concentration entered at the 9th step. This indicates that the initial peak has a much stronger correlation with nephrotoxicity than initial trough concentration. In other models when 48-hour variables were tested, initial peak concentration continued to be the first variable to enter each model while initial trough was excluded. When trough concentrations are maintained in the previously defined 'nontoxic range' (i.e. less than 2 mcg/ml), there is little concentration variability and it cannot be used to discriminate between nephrotoxic and nontoxic patient groups. The fact that initial peak and trough concentrations are significantly correlated (r=0.528) may also prevent the initial trough concentrations to enter the model.

Duration of therapy has also been reported to correlate significantly with aminoglycoside nephrotoxicity in both univariate and multivariate studies.[19,24,27-29] Williams, et al.[19] in the stepwise discriminant analyses of factors associated with nephrotoxicity in patients receiving amikacin noted that days of therapy was the sole factor included in the stepwise discriminant function which was positively correlated with the development of toxicity. However, it is found in this study that duration of therapy although included in Model

N1 at step 4 was again excluded at step 10 due to loss of significant association with the outcome after all other variables entered the model. Examining the results from univariate analysis, duration of therapy was not significantly different between toxic and nontoxic groups with the mean value slightly higher in the nontoxic group. Since this variable reflects the duration of therapy before nephrotoxicity is observed, the relatively short duration of therapy in the toxic group (mean of 6.7 days) suggests that at least some patients developed apparent nephrotoxicity early in the therapy. Indeed, four out of 13 nephrotoxic patients developed nephrotoxicity within the first three days of therapy. Although this is relatively unusual for classical aminoglycosides induced nephrotoxicity, no other identifiable causes could be found to explain the rise of serum creatinine except for one who had preexisting lupus nephritis. True contribution of duration of therapy to the development of aminoglycoside induced nephrotoxicity therefore requires further study with possibly larger sample of nephrotoxic patients.

With regard to the development of nephrotoxicity, sex has been a controversial factor. In studies done previously, most univariate studies have not found a correlation between sex and gentamicin nephrotoxicity. Two multivariate analyses,[33,40] however, have independently found that sex was included in their multivariate models in which females seem to be more prone to the development of nephrotoxicity. This study, indicates that males are more likely to develop nephrotoxicity in the univariate as well as the multivariate

analyses. This opposite finding further complicates the picture of the relationship between sex and nephrotoxicity for which a postulated explanation has never been given. Whether the result is an artifact is not certain since the number of nephrotoxic patients in this study as well as the two previous studies are relatively small. Further investigations will be needed to clarify the possible correlation of sex and aminoglycoside induced nephrotoxicity. Because the results of this study opposed those of previous investigations, sex was excluded from the analysis and Model N3 was developed.

Some studies[22-24] have confirmed that age is a risk factor for the development of nephrotoxicity in patients receiving aminoglycosides though others have not.[25-31] In this patient population, the mean age is 65 years. The results from discriminant analyses (Models N2 and N3) suggest that with all other factors remaining constant, the older the patient, the higher the risk of nephrotoxicity.

Models N2 and N3 also indicate that the higher a patient's initial creatinine clearance, the more likely the patient will develop nephrotoxicity. This is contrary to many previous studies which showed that nephrotoxic patients had higher mean initial serum creatinine along with lower mean initial creatinine clearance and implied that patients with preexisting compromised renal function may be more prone to toxicity. However, this result is consistent with another multivariate study done by Moore, et al.[33] They pointed out that in the previous

studies, doses were not adjusted according to plasma levels and the presence of high serum concentrations in patients with compromised renal function may be the real cause of the toxicity. In patients whose serum aminoglycoside concentrations are in the therapeutic range, those patients with better renal functions may in fact have a higher filtered load of aminoglycoside and their renal tubules are exposed to higher concentrations of aminoglycosides thus leading to a greater risk of nephrotoxicity. Patients whose estimated creatinine clearances are below 15 ml/min/70kg have been excluded in this study and serum gentamicin concentrations were routinely monitored for all patients and maintained in the therapeutic range. As a result, this study supports the idea that when all other factors are controlled, higher creatinine clearance actually predispose patients to greater risk of aminoglycoside induced nephrotoxicity.

Concomitant cephalosporins was another variable included in Model N2. Cephalosporins in combination with aminoglycoside treatment has long been suspected to enhance aminoglycoside induced nephrotoxicity.[36,40] Cephaloridine and cephalothin are the cephalosporins that have been commonly incriminated as enhancing aminoglycoside nephrotoxicity. Due to the lack of definite information on other cephalosporins, all cephalosporins used in the patient population were included in the study. Interestingly, when the 48-hour variables were used, the variable 'concomitant cephalosporins' was included in the discriminant function with a positive association with toxicity. But when sex was

excluded from the 48-hour variables (Model N3), 'concomitant furosemide' instead of cephalosporins entered the model. Furosemide has also been incriminated as a risk factor for the development of aminoglycoside nephrotoxicity.[31,38] There is no readily available explanation for the discrepancy of Model N2 and N3, and since both of these agents were included in Model N1 as well, it is suggested that both concomitant cephalosporins and furosemide may really play a role in enhancing gentamicin nephrotoxicity. Caution therefore should be taken when these agents are used in combination with aminoglycosides.

Models developed for nephrotoxicity analyses were also tested by Jackknife procedure except for Model N1 since this model encompasses relatively large numbers of variables which is difficult to interpret and impractical to use. Jackknife procedures were applied to the simple models (Models N2 and N3). When 10.8% was used as the a priori probability of nephrotoxicity occurring, the cut-off points (1.937 for Model N2 and 2.069 for Model N3) are chosen based on a linear combination of the midpoint of the two centroids and the natural logarithm of the ratio of the prior probabilities of the two groups. As seen in the classification matrices, although both models raised the probability of correctly predicting a new patient to be toxic ($P(G_1/D_1)$) from 10.8% to 60.0% (Model N2) and 50.0% (Model N3), these models can only correctly identify approximately 20% of the known toxic patients ($P(D_1/G_1)$ = 23.1% for Model N2, 15.4% for Model N3), that is to say that these models can overlook a significant number of toxic patients. It

is important to be able to identify nephrotoxic patients, yet the models derived in the manner noted above did not perform as well as had been expected. The a priori probability of toxicity was therefore raised to increase the cost of misclassifying a nephrotoxic patient as a nontoxic patient. By shifting the cut-off point more toward the nontoxic centroid, the probability of misclassifying a toxic patient to be nontoxic can be lowered as depicted in Figure 2. It can also be seen from Figure 2 that by choosing the cut-off point at the midpoint of the two centroids, the total misclassification probabilities can be minimized. As the prior probability of toxicity was raised to 50%, the cut-off point is 0.6332 for Model N2 and 0.5401 for Model N3. While Model N3 was done excluding sex from the analysis, it cannot discriminate toxic from nontoxic patients as well as Model N2 as judged by the canonical correlation. It is therefore thought that Model N2 with 50% prior probability of toxicity is the best model developed in terms of the ability to classify and to predict a nephrotoxic patient as well as the convenience in application.

Besides using a cut-off point to classify or predict a patient's outcome, a cumulative probability curve was also developed for Model N2 with a 50% prior probability of toxicity (Figure 1). This curve allows one to estimate the probability of a new patient developing nephrotoxicity. To illustrate the use of the probability curve and Model N2, the following example is used. A 66 year-old male with initial estimated creatinine of 70ml/min/70kg received gentamicin

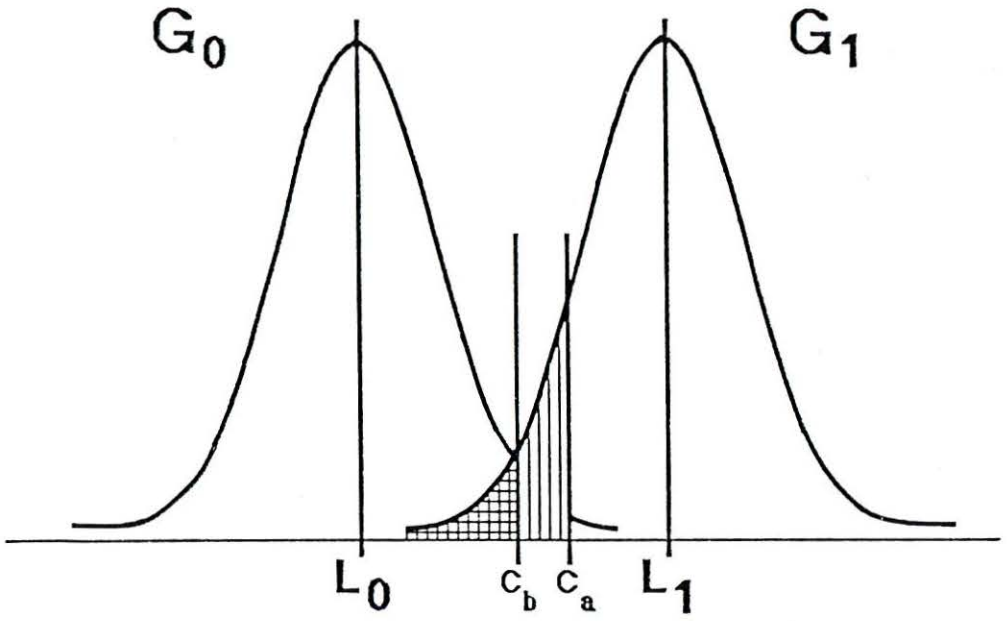

Fig. 2. Theoretical distributions of nontoxic (G_0) and toxic (G_1) groups with L_0 and L_1 being the centroid of each group. Cut-off points C_a = 1.937 is based on prior probability of 10.8% and C_b = 0.6334 is based on prior probability of 50%. Shaded areas represent the probability of misclassifying nephrotoxic patients as nontoxic patients. (▥ : when C_a is used as the cut-off point and ▤ : when C_b is used as the cut-off point)

without other concomitant antibiotics. The initial serum peak gentamicin concentration is 8.5 mcg/ml, the discriminant score = 0.4488 x (8.5) + 1.140 x (1) + 0.01562 x (70) + 0.5940 x (0) + 0.01883 x (66) - 5.246 = 2.045, by plotting this onto the abscissa in Figure 1, the corresponding probability can be found to be about 91% on the ordinate which indicates a high risk of nephrotoxicity development.

Initial peak concentration was included in Models C1, N1, N2 and N3. Based on the findings that initial peak gentamicin concentration does not contribute to the clinical cure positively (Model C1) and yet is positively associated with the nephrotoxicity (Models N1 to N3), one should calculate the initial dose to avoid high initial peak concentrations. It should also be kept in mind that mean peak concentration should be maintained high enough above MIC since this has been found to correlate positively with clinical cure.[19,43] One other finding is that the concomitant use of cephalosporins is positively correlated with nephrotoxicity, while the use of concurrent effective antibiotics which include largely cephalosporins was not found to significantly benefit the clinical outcome of patients (Models C2 and C4), choice of concomitant antibiotics should therefore be made with discretion. In the presence of other risk factors of nephrotoxicity such as high initial peak gentamicin concentration, concomitant use of furosemide and old age, unless synergistic use of cephalosporins and gentamicin is indicated, cephalosporins should be avoided if possible. Sex, age, site of infections, and creatinine clearance are variables

that cannot be therapeutically manipulated, but they may be useful as predictors of patients' clinical outcome or the likelihood of developing nephrotoxicity.

This study is not without limitations. Due to the retrospective nature of the study, various data that may be associated with clinical outcome and nephrotoxicity were not collected. The lack of availability of these other variables may have inhibited the development of more sensitive and specific models. Lack of follow-up data after the patients are discharged from the hospital may also have limited our evaluation of the paitents' clinical outcomes and possible delayed nephrotoxicity. Therefore, if these conditions are altered, the results presented above may not apply.

CONCLUSIONS

Discriminant analysis used as a tool in statistical analyses can reveal the multivariate differences between two or more groups and can further be used for classification purposes as demonstrated above.

Higher body temperature and older age are found to be negatively associated with clinical cure in patients treated with gentamicin in the multivariate analysis. Surgical intervention, on the other hand, appeared to be beneficial to patients' clinical outcomes in patients who need it. Other variables not tested such as MIC, intensity factors, severity of underlying diseases may further aid in the interpretation of the differences in patients' clinical outcomes as well as in the prediction of membership of individual cases.

Male sex, older age, higher creatinine clearance, concomitant cephalosporins and furosemide and most importantly, the high initial peak serum concentration of gentamicin, are found to be able to predispose a patient to nephrotoxicity. Model N2 is especially useful for the purpose of early detection of renal function decline.

Based on these findings, efforts should be made toward balancing clinical cure and nephrotoxicity especially in the elderly when gentamicin is used. At the same time, more multivariate studies should be conducted to disclose the risk factors of clinical failure and

nephrotoxicity in patients treated with gentamicin as well as the pathophysiology of aminoglycoside induced nephrotoxicity.

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